

Diffuse Large B-Cell Lymphoma of the Central Nervous System. Immunophenotype, Clinicopathological Features and Differential Diagnosis

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ABSTRACT

Background: Diffuse large B-cell lymphomas of the central nervous system (DLBCL CNS) represent less than 1% of all lymphomas and between 2% and 3% of all cerebral tumors. They occur in adults of 60 years of age or more. The objective of this work is to describe the clinical-pathological characteristics, the immunophenotype and the differential diagnosis. **Clinical Case:** From the files of the surgical pathology unit we found four cases of primary diffuse large B cell lymphoma of the central nervous system in a 6-year period. Three corresponded to women over 47 years of age and the other to a 42-year-old man. The time of evolution was between 2 and 4 months. The symptoms were headache, blurred vision, hemiparesis, and seizures. Localization was in the pineal region, the frontal, parietal regions, and the right thalamus. Morphologically, large lymphoid cells with a diffuse growth pattern and necrosis were observed. Immunohistochemical markers, such as CD 20 and bcl2 were positive, one was positive to CD3. Expression of bcl6 and CD 10 was positive in one case, and MUM-1 was positive in three cases. All the cases were negative for Epstein-Barr virus. **Conclusions:** The diffuse large-B cell lymphoma of the central nervous system is rare. Its average age of presentation is at 60 years or older. The localization is in the pineal, frontal, parietal and thalamic regions. Three cases were originated by activated B lymphocyte (MUM-1 expression) and other from the Germinal Center (GC) (CD 10 expression). The clinical course was bad. The four patients died shortly after the diagnosis.

Keywords: Primary Lymphoma; Central Nervous System

1. Introduction

Primary lymphomas of the central nervous system are immunophenotype B lymphomas with an aggressive clinical course and, in general, correspond to diffuse large B cell lymphomas and Burkitt's lymphoma. Rare cases of small lymphocyte lymphomas have been reported [1].

The average age of presentation in non-immunocompromised patients is around 60 years, when occurring in patients with HIV syndrome the age of presentation is 5 to 10 years earlier. Symptoms depend on the anatomical location, although they are frequently located in the cerebral hemispheres, around 60% are found in the supratentorial area. [2] Symptoms are focal and/or are caused by the increase in intracranial pressure that can be rapidly progressing.

Radiological studies such as MRI (Magnetic Reso-

nance Image) or CAT (Computed Axial Tomography) scan of the brain reveal heterogeneous lesions with signs of central necrosis; in 20% to 40% of cases, multiple lesions can be observed. Diagnosis is histopathological and tissue can be obtained by either stereotactic biopsy or craniotomy.

Most of these lymphomas present cells that resemble blasts, with a diffuse infiltration pattern and frequently, cells are distributed around the blood vessels, with a concentric pattern accompanied by an increase in reticulin fibers. Most of these tumors can be classified as centroblastic.

They express markers for B cells, such as CD 20, CD 22, or CD 79^a, and an important percentage (89%) express MUM-1.

Prognosis is poor and differential diagnosis must be made from other tumors of the central nervous system.

The objective of this study is to present the clinicopathological, immunophenotype characteristics and the dif-

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ferential diagnosis of this rare type of lymphoma in non-immunocompromised patients.

2. Clinical Cases

In the surgical pathology archives of the Pathology Unit of the General Hospital of Mexico and of the School of Medicine (UNAM), in a 6-year period, we found four patients with a diagnosis of diffuse B lymphoma of large cells with primary presentation at the central nervous system.

In the clinical files we searched for symptomatology, radiological findings, clinical diagnoses, treatment and follow-up.

We reviewed the histological sections stained with hematoxylin-eosin, Schiff's periodic acid, and staining of the reticulum. Immunohistochemical reactions were made manually with the avidin-biotin-peroxidase technique with previous antigenic recovery, for this, we used citrate buffer at 99°C during 10 min in a pressure cooker.

Monoclonal antibodies used were CD 20 (L-26 clone Dako Cytomation), CD 3 (rabbit monoclonal antibodies; Dako Cytomation), CD 10 (clone 56C; Novocastra Laboratories), bcl2 (clone 124; Dako Cytomation), bcl6 (clone PGB6p; Dako Cytomation), MUM 1 protein (clone MUM1p; Dako Cytomation) and LMP-1 (clone Zebra/Dako Cytomation). Diaminobenzidine was used for microscopic evaluation.

From a total of 357 biopsies with diagnosis of diffuse large B-cells lymphoma originated in lymph node, palatine tonsil, digestive tract, and other sites in a 6-year period (2004-2010), we identified four patients whose primary site of origin was the central nervous system (1.1%).

3. Case Reports

3.1. Case 1

Male, 42 years old, immunocompetent. He started with clinical symptoms 4 months before his death. Symptoms were loss of recent memory, paresthesia of lower limbs, then holocranial cephalalgia, nausea, vomiting, blurred vision, and left hemiparesis were added (Table 1). Neuro-

logical exploration revealed altered mediate and immediate memory. MRI revealed a heterogeneous lesion, of irregular borders, neoplastic aspect, in the pineal region as well as ventricular dilation (Figure 1). Therefore, he was subjected to partial resection of the tumor lesions through right parietal craniotomy.

The radiological diagnosis was of an astrocytoma in the pineal region. He evolved torpidly and died during the immediate postoperative period.

The surgical specimen consisted of several irregular fragments of tissue, brown-grayish, that measured as a whole 3 × 2 × 1.3 cm.

Histology revealed a lymphoid neoplasm constituted by large cells, of inconspicuous cytoplasm, ovoid nuclei, discretely pleomorphic, and with nucleoli marginal to the nuclear membrane with a perivascular and concentric disposition (Figure 2), which became more evident with the staining of the reticulum. In Table 2 presents a sum-

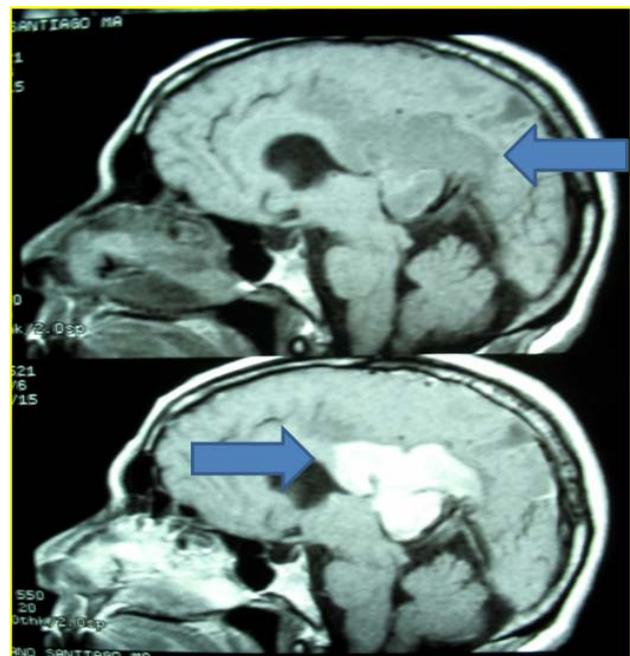


Figure 1. Case 1. MRI of the brain, revealing a heterogeneous lesion of irregular borders in the pineal gland region and ventricular dilation.

Table 1. Radiological characteristics and clinical diagnosis.

Gender	Age	Site	Symptoms	Diagnosis	Type of lymphoma
1. M	42	Pineal	Memory alterations paresthesia, blurred vision	Astrocytoma	DLBCL ABL
2. F	67	Parasagittal and frontal	Hemiparesis, seizures and cephalalgia	Meningioma	DLBCL ABL
3. F	47	Thalamus	Hemiparesis, blurred vision, convulsive crisis and cephalalgia	Glioma vs lymphoma	DLBCL GC Expression to CD 3
4. M	85	Temporal	Dysarthria, monoparesis, right fasciculations	Tumor of the Central Nervous System	DLBCL ABL

M = male; F = female; DLBCL = Diffuse large B-cell lymphoma. ABL Activated B lymphocyte DLBCL GC = Diffuse large B. cell lymphoma originated in the germinal center by immunophenotype.

mary of the immunohistochemical reactions that expressed CD 20, bcl 2, and Mum-1. Bone marrow presented no alterations.

3.2. Case 2

Woman, 67 years, immunocompetent. She started the clinical symptoms two months before she died. Symptom were diminution of muscular strength in the left hemibody, that made deambulation impossible and right cephalgia. Besides she coursed with partial seizures characterized by involuntary movements of the left thoracic member, as summarized in **Table 1**.

Physical exploration revealed psychomotor agitation, understandable speech, disoriented temporally and spatially. She presented left hemiparesis and hyperreflexia and Babinski. MRI (Magnetic Resonance Image) of the brain revealed hyperintense images in T1, in right parasagittal and frontal regions, with perilesional edema that caused diminution of the subarachnoid space toward convexity.

Based on the diagnosis of meningioma of the convexity, right fronto-parietal craniotomy and tumoral resection were performed. She died afterward.

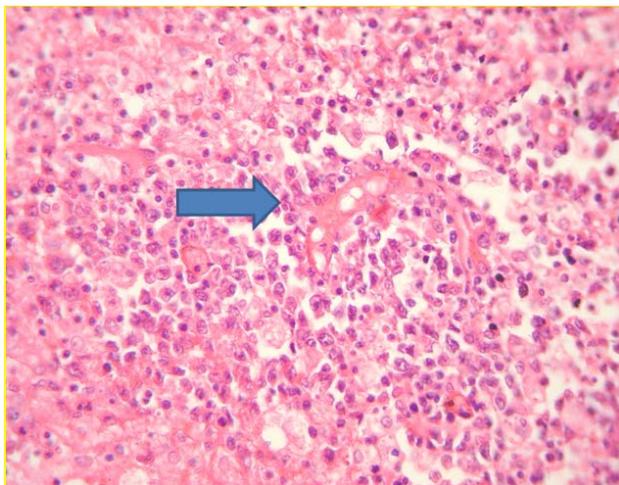


Figure 2. Case 1. Large lymphoid cells, nuclei with evident nucleoli and perivascular disposition can be identified morphologically (10× H-E).

Surgical specimen consisted of several fragments of soft-consistency, white-grayish tissue that showed areas of necrosis and as a whole measured 5 × 3 × 2 cm.

Histology revealed a lymphoid neoplasm constituted by large cells with a more or less evident cytoplasm, irregular ovoid nuclei, marginal nucleoli, split nuclei with an evident single nucleoli; disposition of cells was diffuse and perivascular and became evident by staining the reticulum (**Figure 3**).

Immunohistochemical reaction such as CD20 and bcl2 were positive in the membrane of neoplastic cells and Mum-1 was positive in the nuclei of the neoplastic cells. CD3, CD10, bcl6 and LMP-1 were negative, as indicated in **Table 2**. Bone marrow without alterations.

3.3. Case 3

Woman, of 47 years of age, who presented blurred vision of the left eye, with 2 months of evolution; then, left hemiparesis, right fronto-parietal cephalgia, and convulsive crisis were added. Physical exploration revealed visual hallucinations, papilledema, right facial hemiparesis. Laboratory tests revealed no alterations. MRI revealed a heterogeneous image at the level of the right thalamus measuring 3 × 1.5 cm.

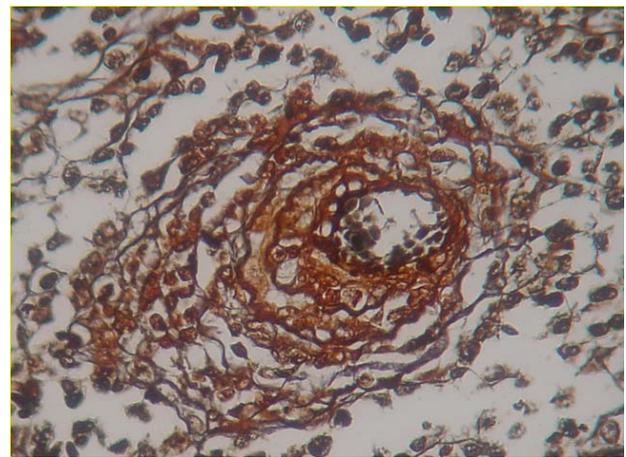


Figure 3. Case 2. Staining of the reticulum evidences the concentric disposition of the tumor cells (10× reticulum staining).

Table 2. Morphology and immunophenotype characteristics of primary DLBCL of the CNS.

No. of case	Morphology	Immunophenotype
1.	CB, necrosis, perivascular pattern	CD 20+, CD 3-, Mum-1+, CD 10-, bcl2+, bcl6-, LMP-1-
2.	CB, reactive gliosis, perivascular pattern	CD 20+, CD 3-, Mum-1+, CD 10-, bcl2+, bcl6-, LMP-1-
3.	CB, perivascular pattern	CD 20+, CD 3+, Mum-1-, CD 10+, bcl2+, bcl6+, LMP-1-
4.	CB, focal perivascular pattern	CD 20+, CD 3-, Mum-1+, CD 10-, bcl2+, bcl6- LMP-1-

CNS = Central Nervous System; DLBCL = Diffuse large B-cell lymphoma; CB = Centroblastic. LMP-1 (Latent membrane protein of the Epstein-Barr virus); M = male; F = female; DLBCL = Diffuse large B-cell lymphoma. ABL Activated B lymphocyte DLBCL. GC = Diffuse large B. cell lymphoma originated in the germinal center by immunophenotype.

Clinical diagnosis was of glioma vs basal nuclei lymphoma, as indicated in **Table 1**. Cerebral biopsy was performed through stereotaxy.

Morphologically it was similar to the two previous cases, however many of the neoplastic cells expressed CD 20 and CD 3 (**Figures 4 and 5**), as well as germinal center markers (CD 10 and bcl6) as shown in **Table 2**. Biopsy of the bone marrow revealed myelofibrosis grade I, without infiltration.

The patient evolved well after high doses of intravenous methotrexate (10 doses of 25 mg) and rescue with folinic acid 24 h afterward. Clinical follow up was of 4 months, with persistence of cephalalgia and eventual death.

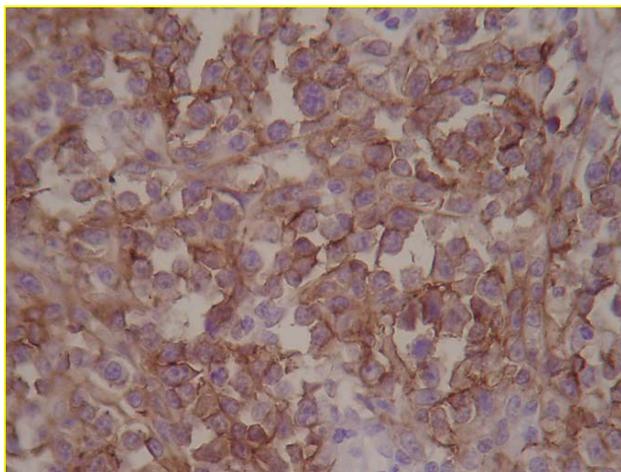


Figure 4. Case 3. Anti-CD 30 immunohistochemical reaction that is positive in the cytoplasmic membrane of the neoplastic cells (40× Immunoperoxidase).

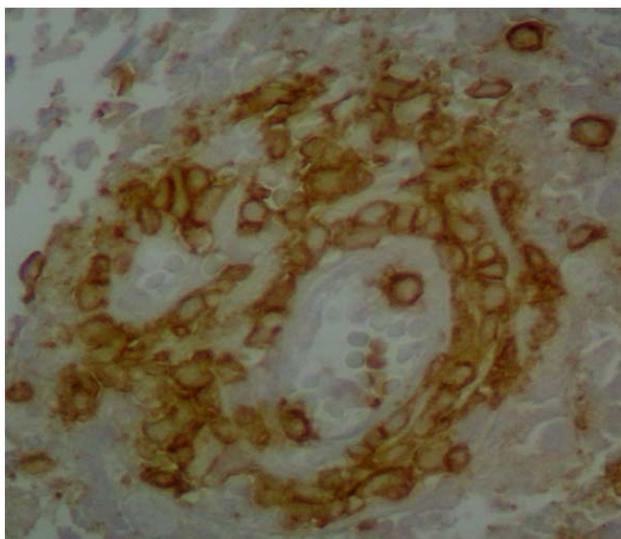


Figure 5. Case 3. Aberrant expression of CD 3 in neoplastic cells that are distributed around the blood vessels (40× Immunoperoxidase).

3.4. Case 4

Woman of 85 years, with antecedents of systemic arterial hypertension and chronic obstructive pulmonary disease. She started with clinical symptoms one month before diagnosis. Symptoms were dysarthria, right monoparesis and facial fasciculations of the same side. Simple CAT scan of the brain and MRI revealed left parietal tumor (**Figure 6**), craniotomy was performed based on a clinical-radiological diagnosis of tumor of the central nervous system, as indicated in **Table 1**. Partial resection of the tumor was performed through craniotomy.

Several irregular fragments of tissue measuring $4 \times 3 \times 2$ cm were received. Histology revealed a lymphoid tumor constituted by large cells, scarce cytoplasm, and irregular nuclei perivascularly distributed. Immunohistochemical markers were positive for CD 20, bcl2, and MUM-1 (**Table 2**). Post-operative period with clinical evolution of three months and eventual death.

4. Discussion

Primary lymphomas of the central nervous system (PLCNS) are non-Hodgkin extranodal lymphomas that occur in the craniospinal axis and most are highly malignant type B neoplasms [1,2]. They present at this site probably due to the tropism of lymphoid cells [3]. The biological mechanism of selective tropism is still unknown, and the genesis of this lymphoma in the central

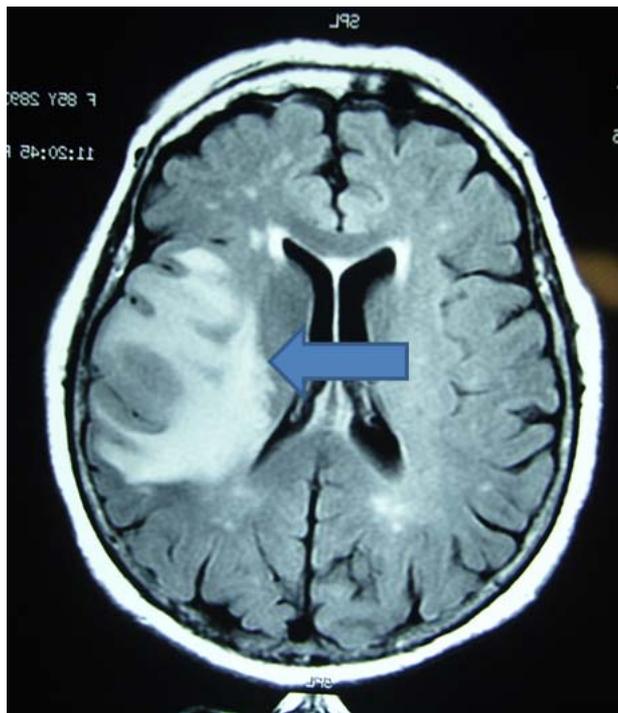


Figure 6. Case 4. MRI revealing a hyperintense homogeneous image, at the fronto-parietal level.

nervous system is not completely understood; a probable hypothesis is that the tumor cells originate in extracranial sites [4].

The immunophenotype and the presence of rearranged, somatically mutated immunoglobulin (IG) genes with evidence for ongoing mutation suggest PCNSL tumor cells are derived from a germinal centre (GC) exit B cell [5]. Tumor manifestation is often diffuse, multifocal and frequently affects the supratentorial cerebral parenchyma. They occur in all age groups, with an incidence peak in the fifth or sixth decade of life in patients without AIDS [6]. In the present study, in a period of 6 years, four patients presented as primary site of the diffuse large B-cells lymphoma (DLBCL) the central nervous system, representing 1.1% of all the diffuse large cell lymphomas at diverse sites, including the lymph node, in our institution. Average age was of 60 years, being more frequent in women, which agrees with the corresponding literature of the American continent; other authors have found men to be more affected [7,8].

Clinical symptomatology cured 2 to 4 months before the diagnosis, hence the start is fast with just a few months before diagnosis. In the series by Bataille *et al.*, the most common symptoms were neurological focality (70%) and neuropsychiatric alterations (43%); [9] in the present study, these were cephalaea, hemiparesis, visual alterations and convulsive crises. The site most affected is the frontal lobe; in this series location was variable presenting in the pineal region, frontal lobe, parasagittal region, temporal lobe, and in the thalamic region, as summarized in **Table 1**. In more than half the cases, lesions are solitary (65%), although multifocal lesions can be observed (35%) [10,11]. The CAT scan reveals isodense and hyperintense lesions, and with MRI they appear isointense and hypointense and can present perilesional edema and mass effect. In our patients, these changes in MRI were heterogeneous, without a predominating pattern, lesions were localized in three, and one showed multifocal lesions. DLBCLs presenting in the CNS are generally intraparenchymatous and with periventricular affection, the latter is a very important piece of information for the differential diagnosis between primary and secondary lymphomas, since the latter affect mainly the leptomeninges [12]. Morphologically, neoplastic cells are large, barely evident cytoplasm and nuclei that resemble centroblasts, as can be seen in **Figure 2**, although they can exhibit an immunoblast morphology [1] with a diffuse growth pattern and perivascular disposition and concentric accentuation (**Figure 3**), tumor cells alternate with small reactive lymphocytes, macrophages, activated microglial cells, and reactive astrocytes [13].

They express pan-B markers such as CD 20 and CD

79^a (**Figure 4**), they can express bcl2 and CD 10, not related to t (14; 18) (q32; q21). Expression of bcl-6 has been associated with a favorable prognosis. However, strong expression of RF4/MUM-1 has been observed in approximately 90% of cases [14,15].

Our results agree with previously reported data in other series. DLBCLs in the SNC frequently contain complex cytogenetic anomalies, diagnosis is based on the combination of histology, immunophenotype, and molecular clonality [16].

The aberrant expression of B-cell-associated antigens has been identified in benign proliferations of T cells and non-Hodgkin lymphomas with the immunophenotype T [17,18]. It is not rare that low-grade non-Hodgkin lymphomas co-express T-cell-associated antigens, particularly CD 5 and CD 43 [19,20]. There are T markers, such as CD 5, that are expressed in DLBCL without any other specification in lymph node and in other variants like large cell intravascular lymphomas [21,22]. Cases of B lymphomas with aberrant co-expression to T cell-associated antigens, such as CD2, CD 4, CD 7, CD 8, and CD 45 RO have been reported [23-25]. In a recent study, Wang *et al.* [26] found four cases of DLBCL with aberrant expression to CD 3, in one of the cases, the lymphoma occurred in the CNS in a 52-year-old woman; in the present study, expression of CD 3 was observed in a 47-year-old woman (Case 3) (**Figure 5**); the biological significance and the mechanism for the CD 3 expression in DLBCL is not known; hence, we believe that other pan B markers such as CD 79^a, CD 138, PAX 5, and Mum-1 must be determined or molecular biology techniques must be implemented for the correct determination of the cell lineage of these unusual lymphomas. In the present series, three DLBCL in the SNC expressed Mum-1 and all expressed bcl-2 markers of bad prognosis; in a recent publication of 17 cases, expression of bcl2 and STAT-3 (Signal transducer and activator of transduction) was studied, emphasizing the low expression of this marker as a subtype of diffuse large B cell lymphoma originated from activated lymphocytes [27].

Among the most significantly up-regulated genes in PCNSL were SPPI, TF, DDR1, TUBB2B, SERPINA3, S100B, and CA2. More than 460 expressed sequence tags were differentially expressed between PCNSL [27]. Regarding prognosis, several variables have been identified that affect survival negatively such as: age over 60 years, high serum levels of lactic dehydrogenase, hyperproteinorachia, and affection of deep cerebral structures like periventricular regions, basal ganglia, brain stem, and cerebellum [28].

Differential diagnosis must be made with multiform glioblastoma, primary neuroectodermic tumor, metastases of anaplastic carcinoma and melanoma. Immunohis-

tochemistry with the follow monoclonal antibodies: cytokeratin, HMB 45, acid glial glycoprotein, epithelial membrane antigen and CD 99 are highly valuable for the correct classification of this type of neoplasia [1].

Regarding treatment, a better survival has been shown with the combination of two treatments (methotrexate and radiotherapy) at not too high doses to avoid or reduce the neurological sequelae of these treatments [29].

In conclusion, we present the clinicopathological characteristics of four cases of DBCL in the CNS, three of them classified as originating from activated lymphocyte B, and the other from the germinal center (GC) with aberrant expression of CD3 (pan-T marker).

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Abbreviations

DLBCLCNS = Diffuse Large B Cell Lymphoma of the Central Nervous System.
HIV = Human Immunodeficiency Virus
CNS = Central Nervous System
DLBCL = Diffuse Large B-Cell Lymphoma
CB = Centroblastic
LMP-1 = Latent Membrane Protein of the Epstein-Barr Virus

MRI = Magnetic Resonance Imagen
CAT = Computarizade Axial Tomography
M = Male
F = Female
DLBCL = Diffuse Large B-Cell Lymphoma.
ABL = Activated B Lymphocyte DLBCL
GC = Diffuse Large B. Cell Lymphoma Originated in the Germinal Center by Immunophenotype